Trends in the Content and Use of Oral Contraceptives in the United States, 1964–88

ABSTRACT

Drug marketing and physician survey data were used to examine trends in the use and hormonal content of oral contraceptives in the United States between 1964 and 1988. Retail prescriptions for oral contraceptives peaked at approximately 68 million in 1973 and have remained between 50 million and 60 million since 1981. Despite this relative consistency in the number of prescriptions, physician "mentions" of oral contraceptives have increased by approximately 75 percent. This increase may reflect closer monitoring of women on oral contraceptives. Use of multiphasic formulations has steadily risen, accounting for 37 percent of the oral contraceptive prescriptions in 1988. Mean estrogen and progestin doses in all types of formulations have steadily declined. A change in the type of estrogen and progestin used in preparations has coincided with this decline in dose. The association between age and use of high-dose formulations seen in the past was no longer evident in 1988. The data demonstrate that oral contraceptive formulations in wide use today differ in hormone content from those of the past, when most of the major studies addressing the risks associated with oral contraceptive use were completed. There is therefore a need to determine the risks and long-term effects associated with these newer formulations. (*Am J Public Health* 1991; 81:90–98)

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Introduction

Since oral contraceptives were introduced three decades ago, 56 brands representing 33 unique formulations have been marketed in the United States (see Appendix). Most of these preparations have contained a constant amount of estrogen and progestin (*monophasic* combinations); other types are *sequential*, progestin only ("*minipills*"), and *multiphasic* formulations.

Sequential formulations contained estrogen alone during the first 14 to 16 days of use each cycle followed by an estrogen-progestin combination during the last five to seven days of use. These pills are no longer marketed but were available from 1965 to 1976. Minipills were first introduced in 1972 and have never accounted for more than a fraction of a percent of retail oral contraceptive prescriptions. Multiphasic formulations contain varying estrogen and/or progestin amounts during the cycle and were first introduced in 1982 in an attempt to emulate hormone fluctuations of the menstrual cycle and to lower overall hormone doses.

In considering the beneficial and adverse effects associated with specific oral contraceptive formulations, one must consider the types and doses of estrogen and progestin they contain. Two types of estrogen and nine synthetic progestins have been used in oral contraceptives. The two estrogens, ethinyl estradiol and mestranol, have identical biological effects. Some studies, mostly animal, suggest that on a weight-by-weight basis, ethinyl estradiol is more potent than mestranol in suppressing ovulation, since mestranol must first be converted in the body to ethinyl estradiol.[1–3] In the human body, however, differences in potency between ethinyl estradiol and mestranol do not appear to be important.[4] Progestins contained in oral contraceptives differ by orders of magnitude in potency and may demonstrate varying degrees of androgenic, estrogenic, antiestrogenic, and other metabolic effects.[5–7]

This paper reports changes in the use of oral contraceptive formulations in the United States from 1964 to 1988. It also examines the relationship between formulation type and the age of users in the period 1980–88. An understanding of these trends is important to better interpret results of previous studies and to plan future studies that seek to clarify the relationship between oral contraceptive use and its potential to cause adverse as well as beneficial effects.

Methods

Sources of Data

Data from two pharmaceutical marketing research data bases produced by IMS America, Ltd. (Plymouth Meeting, PA), were used to examine trends in oral contraceptive use and prescribing. The National Prescription Audit (NPA) was used to provide information on the number or oral contraceptive prescriptions

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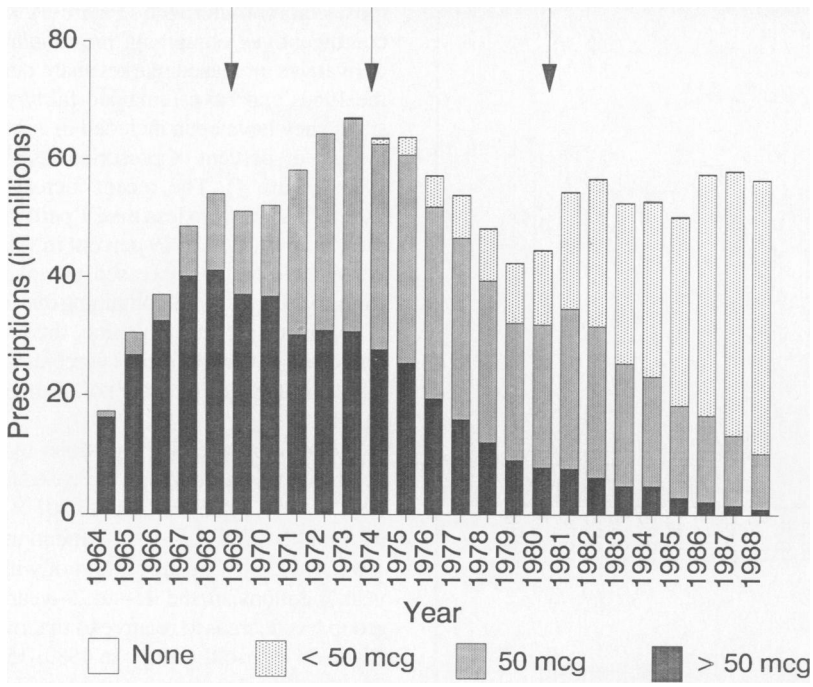

FIGURE 1—Number of Retail Oral Contraceptive Prescriptions by Estrogen Dose, 1964–1988, United States

Arrows indicate points at which changes in data collection methods occurred.

dispensed by retail pharmacies in the contiguous United States. Age-related trends in utilization were based on the National Disease and Therapeutic Index (NDTI) for the years 1980, 1984, and 1988.

The NPA derives its information from chain and independently owned retail pharmacies in the contiguous United States. Other dispensing outlets such as mail order pharmacies, supermarket pharmacies, and clinics are not included. IMS America estimates that retail pharmacies fill approximately 90 percent of prescriptions in the United States. This proportion, however, may not apply to oral contraceptive prescriptions, because approximately one in four women who use reversible forms of contraception rely on publicly funded clinics for care.[8] We were therefore unable to estimate the percentage of oral contraceptive prescriptions that is covered by this study. Nonetheless, previous studies have suggested that trends in oral contraceptive use reported by NPA accurately reflect trends in the general population.[9,10]

From 1981 to 1987, IMS audited all new and refilled prescriptions dispensed at 1,200 computerized pharmacies. This sample was expanded to 2,500 sites in 1987. From 1974 to 1980, data were derived from a representative sample of 800 pharmacies, each of which was audited for two days per month. From 1970 to 1974, 400 pharmacies were audited for four days per month. Prior to 1970, 200 pharmacies reported every fifth prescription filled during the first and third week of each month. Although these changes in methodology may create artifacts at points of change, trends within intervals are unaffected.

Information on the NPA sampling frame is updated annually. Sampled pharmacies represent the universe of retail pharmacies in terms of ownership type, size, and geographic region. Using sampling fractions based on these factors, the number of retail prescriptions dispensed nationwide was estimated.

The NDTI, used to provide information on physician usage patterns of oral contraceptives in relation to age of patients, is based on a sample of 2,130 physicians per quarter recruited from the membership rolls of the American Medical Association and the American Osteopathic Association. The NDTI sample is selected from four geographic regions and 19 specialties, and it is estimated that its sampling universe includes the prescribing practices of 270,827 office-based physicians, but not the prescribing of 51,112 other clinic- and hospital-based physicians. Projection factors derived from the number of physician-days for each of the defined geographic and specialty strata are used to project national estimates.

NDTI-audited physicians are asked to report on each private patient seen or contacted by phone during a specified 48-hour period. Physicians provide information on patient demographics, diagnoses, and treatments for each diagnosis rendered. By convention, the term "mention" is used to denote each drug considered or given during a patient contact. Drugs that are mentioned during a physician-patient contact may reach the patient through prescription, hospital order, provision of samples, or administration or dispensing in the office. It is worthwhile to note that mention of a drug does not necessarily mean that a prescription was issued. Projection factors derived from the number of physician-days in the sample relative to that of the universe for each of the geographically and specialty-defined strata are used to estimate national usage patterns.

Classification of Oral Contraceptives

Formulations were classified by type (monophasic, multiphasic, sequential, minipill), estrogen dose, estrogen contained (mestranol, ethinyl estradiol, none), progestin dose, and progestin contained. Progestins were grouped as follows: norethindrone, ethynodiol diacetate and norethindrone acetate (norethindrone derivative), norethynodrel (oral contraceptives containing norethynodrel were no longer marketed for contraception after October 1988) norgestrel, levonorgestrel, and progestins no longer used in current oral contraceptive formulations (dimethisterone, chlormadinone, medroxyprogesterone acetate). Norethindrone, ethynodiol diacetate, and norethindrone acetate were grouped because previous studies have suggested that these progestins demonstrate similar biological activity and are equally potent on a weight-by-weight basis.[11] We evaluated dose trends by examining both the percentages of retail prescriptions that contained more than 50 μg, 50 μg, and less than 50 μg of estrogen and the mean estrogen and progestin doses of oral contraceptive.

Results

As depicted in Figure 1, total prescriptions rose between 1964 and 1968. After a small decline in 1969, the annual number of prescriptions increased, peaking in 1973. From 1974 to 1979, the number of prescriptions declined steadily. The

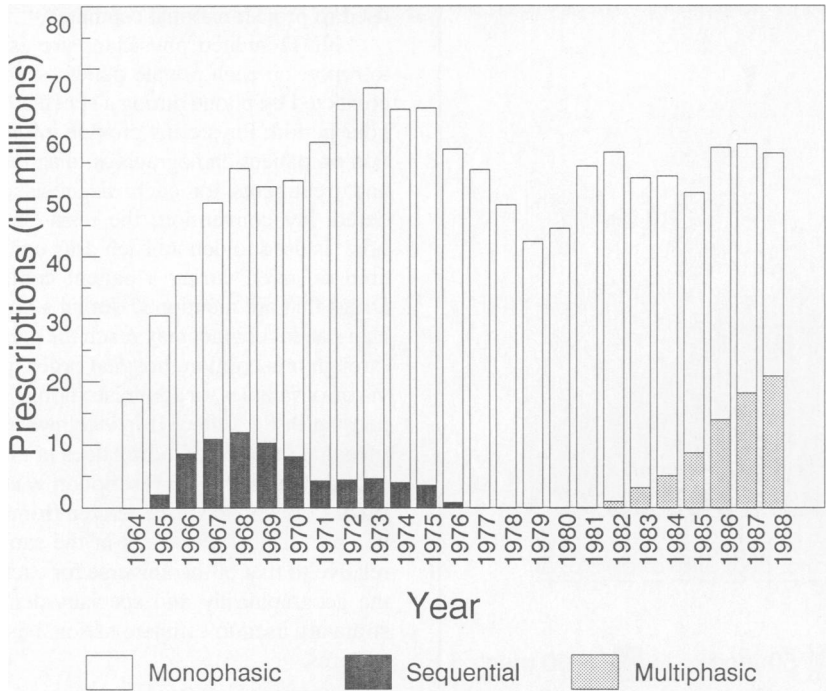

FIGURE 2—Number of Retail Oral Contraceptive Prescriptions by Formulation Type, 1964–1988, United States

TABLE 1—Mean Progestin and Estrogen Dose in Prescriptions for Every Fourth Year between 1964 and 1988, United States

	Progestins				Estrogens	
Year	Norethindrone Group mg	Norgestrel mg	Norethynodrel mg	Levonorgestrel mg	Ethinyl Estradiol μg	Mestranol μg
1964	2.52	—	5.18	—	50[a]	91
1968	1.50	0.50	3.71	—	70	89
1972	1.22	0.50	3.93	—	56	82
1976	1.14	0.46	3.77	—	47	76
1980	1.01	0.41	3.92	—	41	66
1984	0.97	0.37	3.27	0.15	37	62
1988	0.89	0.35	2.73	0.11	35	57

[a]There were only two formulations containing ethinyl estradiol in 1964 (Norlestrin 2.5 mg and Provest), each of which contained 50 μg ethinyl estradiol.
SOURCE: National Prescription Audit, IMS America, Ltd., Plymouth Meeting, PA.

apparent increase in the number of dispensed prescriptions that is seen between 1980 and 1981 could be an artifact of a change in data collection methods that coincided with these dates. Since 1981, the number of prescriptions has remained between 51 million and 58 million.

Prescriptions demonstrate a distinct trend toward use of formulations that contain less than 50 μg of estrogen per tablet (Figure 1). In 1968, fewer than 1 percent of the estimated 54 million retail prescriptions for oral contraceptives were for formulations containing less than 50 μg of estrogen, whereas in 1988 approximately 82 percent of the approximately 57 million retail prescriptions were for formulations with less than 50 μg of estrogen. Retail prescriptions for sequential formulations (no longer marketed) reached their maximum in 1968 (Figure 2). The number of prescriptions for multiphasic formulations steadily increased after they were introduced in 1982, accounting for 37 percent of all retail oral contraceptive prescriptions in 1988.

Mean estrogen and progestin doses have declined over time (Table 1). Since 1981, ethinyl estradiol has become
most common estrogen (Figure 3). C
contraceptives containing norethindr
derivatives increased market share dur
the 1960s and have remained fairly c
stant; they have been included in appr
imately 65 percent of prescriptions si
1970 (Figure 4). The recent increase
levonorgestrel from less than 1 percen
the market in 1982 to 19 percent in 198
attributable to the increased use of t
triphasic preparations containing this fo
of progestin. At the same time, the use
norgestrel declined from 32 percent of
market in 1983 to 16 percent of the mar
in 1988.

Oral contraceptive mentions by
fice-based physicians have increased fr
1980 to 1988 by 75 percent (13,501 ×
mentions in 1988; 7,716 × 10^3 mention
1980: Table 2). The proportion of with
year mentions in the 15- to 24-year-
group has decreased relative to that of
25- to 34-year-old group. In 1980, 15-
24-year-old women accounted for 57 p
cent of oral contraceptive mentions a
25- to 34-year-old women accounted for
percent of mentions. In 1988, these figu
were 48 percent and 45 percent, resp
tively. Mentions in the 35- to 44-year-
group accounted for 6 to 7 percent of m
tions during this interval.

Mentions for multiphasic formu
tions increased between 1984 and 19
(Table 2). In 1984, 15 percent of mentic
were for multiphasic formulations.
1988, 40 percent of mentions were for m
tiphasics. The largest use of multiphas
occurred in the 15- to 24-year-old a
group.

The mean estrogen dose of mentic
was directly associated with age of us
in 1980 and 1984 (Table 3). The associati
between age and ethinyl estradiol dc
was no longer evident in 1988; the avera
ethinyl estradiol dose in mentions was
μg, irrespective of age. The associati
between age and mestranol dose h
weakened. In 1988, the mean mestra
dose for 15- to 24-year-old women was
μg, for 25- to 34-year-old women it was
μg, and for 35- to 44-year-old women
was 63 μg.

In 1980 and 1984, 35- to 44-year-
oral contraceptive users were more lik
to use mestranol-containing formulatic
than their younger counterparts. By 19
only 8 percent of mentions in 35- to
year-old women were for mestranol-c
taining formulations. This figure compa
with 15 percent in 25- to 34-year-
women, and 6 percent in 15- to 24-year-
women.

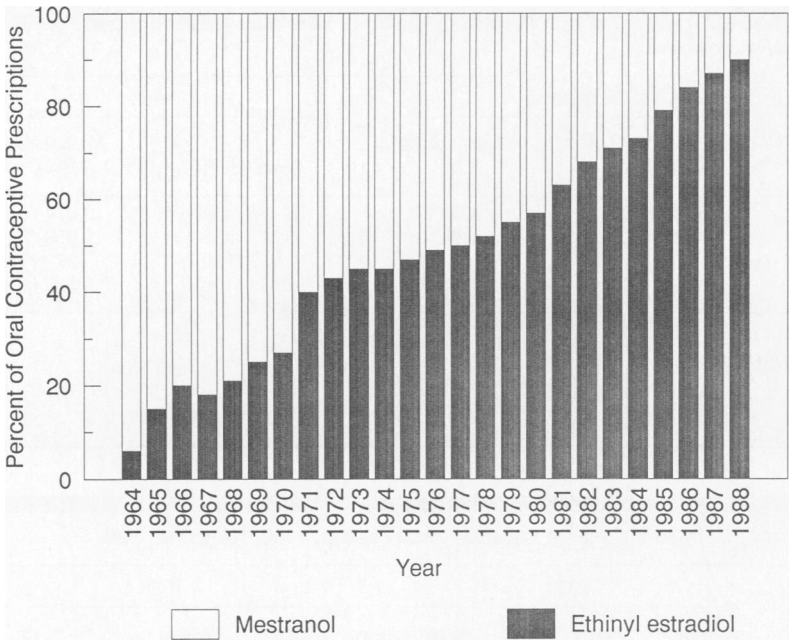

FIGURE 3—Percent of Dispensed Prescriptions by Estrogen Type, United States

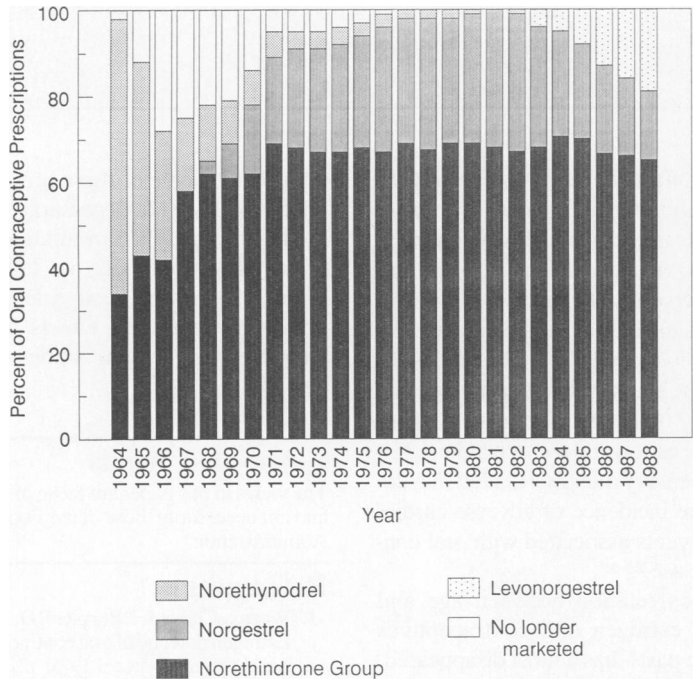

FIGURE 4—Percent of Dispensed Prescriptions by Progestin Type, United States

Discussion

Data presented in this paper pertain to office-based physicians and exclude public clinics as a source of oral contraceptives. In addition, NPA data reflect the number of dispensed retail prescriptions but do not contain information on the number of cycles covered by each prescription. Therefore, NPA data cannot be used to estimate the prevalence of oral contraceptive use in the population. An additional limitation is that there has been no adjustment for change in the number of women of childbearing potential in the population. Despite these limitations, NPA and NDTI data are useful for monitoring large changes in the use of various oral contraceptive formulations over time.

Retail prescription data suggest that overall use of oral contraceptives has been fairly stable since 1981. NPA projections suggest a modest 2.4 percent increase from 1982 to 1987, compared with an 18.5 percent increase in the prevalence of oral contraceptive use reported by Forrest and Fordyce.[12] (Forrest and Fordyce report the percent distribution of women using oral contraceptives increased from 27 percent in 1982 to 32 percent in 1987.) However, neither of these estimates allows for sampling variation, and if we were to estimate the percent change in NPA from 1983 to 1987, a 10.3 percent increase would be noted. This inference, of course, is based on the assumption that both estimates are representative and unbiased and that the average duration of NPA prescription has remained constant over the time interval. However, direct comparisons between NPA projections and those offered by Forrest and Fordyce may not be justifiable, because the former refer to the number of retail prescriptions and the latter are based on self-reported use. Thus, these data are not fully comparable.

Although the number of dispensed retail prescriptions has been relatively stable, the number of NDTI mentions has increased by 75 percent. This apparent inconsistency may be the result of changes in survey methodology, or survey inaccuracy, or it may reflect a change in physician care of patients taking oral contraceptives. We speculate that the observed increase in mentions with no large increase in the number of dispensed prescriptions could be indicative of closer monitoring of women on oral contraceptives.[13]

The impact of the steady increase in the use of multiphasic formulations is unclear because the risks and benefits associated with them compared with other low-dose formulations are largely unknown. Although one article reported a series of functional ovarian cysts in women using multiphasic oral contraceptives,[14] previous studies have demonstrated a reduction in the incidence of

TABLE 2—Number of Mentions of Oral Contraceptives (in Thousands) with Percent of Mentions That Were for Multiphasic Formulations, by Age for 1980, 1984, and 1988, United States

Age (yrs)	1980 Total (%)[a]	1980 Multiphasics (%)[b]	1984 Total (%)[a]	1984 Multiphasics (%)[b]	1988 Total (%)[a]	1988 Multiphasics (%)[b]
15–24	4,412 (57)	NA	5,878 (52)	1,009 (17)	6,475 (48)	3,074 (48)
25–34	2,859 (37)	NA	4,741 (42)	636 (13)	6,147 (45)	2,039 (33)
35–44	445 (6)	NA	577 (5)	43 (7)	869 (7)	272 (31)
15–44	7,716 (100)	NA	11,196 (100)	1,688 (15)	13,501 (100)	5,385 (40)

[a]Percent of total oral contraceptive mentions.
[b]Percent of within-age mentions that were for multiphasic formulations.
NA = Not Available

SOURCE: NDTI, IMS America, Ltd., Plymouth Meeting, PA.

TABLE 3—Mean Estrogen Dose of Mentions by Estrogen Type and Age of Patients, United States, 1980, 1984, and 1988

Age (yrs)	1980 Mean EE Dose µg	1980 Mean ME Dose µg	1980 % of Mentions Containing ME	1984 Mean EE Dose µg	1984 Mean ME Dose µg	1984 % of Mentions Containing ME	1988 Mean EE Dose µg	1988 Mean ME Dose µm	1988 % of Mentions Containing ME
15–24	39	61	31	35	58	17	35	56	6
25–34	40	64	41	37	61	23	35	54	15
35–44	43	69	53	41	69	22	35	63	8
15–44	40	63	46	36	60	80	35	55	10

EE = ethinyl estradiol;
ME = mestranol

SOURCE: NDTI, IMS America, Ltd., Plymouth Meeting, PA.

functional ovarian cysts in women using high- and intermediate-dose formulations.[15,16] No study to date has measured the risk of functional ovarian cyst formation in users of multiphasic formulations relative to nonusers or to women using other low-dose formulations. Gaspard and Lepot have reported no significant difference in follicular development between users of a low-dose monophasic formulation and its triphasic analog.[17]

Progestin doses have been declining over time. However, all progestins are not equipotent on a milligram-per-milligram basis. For example, previous studies suggest that norgestrel is 5 to 10 times as potent as norethindrone, and levonorgestrel is 10 to 20 times as potent as norethindrone.[10] Using these factors to adjust mean dose, today's norgestrel and levonorgestrel doses are comparable, in terms of potency, to norethindrone doses of the 1960s and 1970s (Table 1). In addition, norgestrel and levonorgestrel may demonstrate more androgenic activity than norethindrone derivatives.[18] Changes in oral contraceptive progestins may have effects on ratios of high- to low-density lipoproteins,[19] glucose tolerance, blood pressure,[20] and the risks of vascular disease,[21–23] benign breast disease,[24] and perhaps even breast cancer.[25]

A decline in the mean estrogen dose contained in formulations was observed. Because the intravascular coagulation and the activity of several clotting factors appear to be estrogen dose dependent,[26–28] this decline has probably resulted in a decline in the incidence of adverse cardiovascular events associated with oral contraceptive use.[29–31]

The correlation between age and high-dose estrogen oral contraceptives seen in the past[32] has almost disappeared. For the most part, women of older reproductive age who choose to use oral contraceptives have taken advantage of the risk reductions associated with low-dose estrogen formulations.

Our data confirm that the oral contraceptives of today contain less hormone than those of the past, when most of the major studies that addressed the risks associated with oral contraceptive uses were completed. Some of these previously defined risks may not necessarily be associated with today's formulations. Additional risks, if any, are not fully known. There is therefore a need to determine the acute and long-term effects associated with these newer formulations. □

Acknowledgments

The views in this paper are those of the authors and not necessarily those of the Food and Drug Administration.

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APPENDIX— Hormonal Content of Oral Contraceptives Marketed in the United States, 1964–88

Brand	Years	Progestin	mg[a]	Estrogen	μg[a]
Monophasics					
Brevicon	1975–88	NEI	0.5	EE	35
Demulen 1/35	1982–88	ETH	1.0	EE	35
Demulen 1/50	1970–88	ETH	1.0	EE	50
Enovid 10 MG	1964–87	NEY	10.0	ME	150
Enovid 5 MG	1964–88	NEY	5.0	ME	75
Enovid-E	1964–88	NEY	2.5	ME	100
Genora 0.5/35	1988–88	NEI	0.5	EE	35
Genora 1/35	1987–88	NEI	1.0	EE	35
Genora 1/50	1987–88	NEI	1.0	ME	50
Gynex 0.5/35	1988	NEI	0.5	EE	35
Gynex 1/35	1987–88	NEI	1.0	EE	35
Levlen	1986–88	LEV	0.15	EE	30
Loestrin 1.5/30	1973–88	NEA	1.5	EE	30
Loestrin 1/20	1973–88	NEA	1.0	EE	20
Lo/Ovral	1975–88	NOR	0.3	EE	30
Modicon	1975–88	NEI	0.5	EE	35
Nelova 0.5/35	1988–88	NEI	0.5	EE	35
Nelova 1/35	1987–88	NEI	1.0	EE	35
Nelova 1/50	1988–88	NEI	1.0	EE	50
Nordette	1982–88	LEV	0.15	EE	30
Norethin 1-35E	1988–88	NEI	1.0	EE	35
Norethin 1-50E	1988–88	NEI	1.0	EE	50
Norinyl 1/35	1980–88	NEI	1.0	EE	35
Norinyl 1/50	1967–88	NEI	1.0	ME	50
Norinyl 1/80	1969–88	NEI	1.0	ME	80
Norinyl 2 mg	1964–88	NEI	2.0	ME	100
Norlestrin 1 mg	1967–88	NEA	1.0	EE	50
Norlestrin 2.5 mg	1964–88	NEA	2.5	EE	50
N.E.E. 1/35	1988–88	NEI	1.0	EE	35

(Continued)

APPENDIX—Continued

Brand	Years	Progestin	mg[a]	Estrogen	μg[a]
Ortho-Novum 10 mg	1964–80	NEI	10.0	ME	60
Ortho-Novum 1/35	1980–88	NEI	1.0	EE	35
Ortho-Novum 1/50	1967–88	NEI	1.0	ME	50
Ortho-Novum 1/80	1968–88	NEI	1.0	ME	80
Ortho-Novum 2 mg	1964–88	NEI	2.0	ME	100
Ovcon-35	1976–88	NEI	0.4	EE	35
Ovcon-50	1976–88	NEI	1.0	EE	50
Ovral	1968–88	NOR	0.5	EE	50
Ovulen	1968–88	ETH	1.0	ME	100
Provest	1964–69	MED	10.0	EE	50
Zorane 1/20	1974–77	NEA	1.0	EE	20
Zorane 1.5/30	1974–79	NEA	1.5	EE	30
Zorane 1/50	1973–77	NEA	1.0	EE	50
Sequential Formulations					
C-Quens	1965–72	CHL	2.0	ME	80
Noriday	1968–69	NEI	1.0	ME	50
Norquen	1967–76	NEI	2.0	ME	80
Oracon	1965–76	DIM	25.0	EE	100
Ortho-Novum SQ	1967–76	NEI	2.0	ME	80
Progestin Only Formulations					
Micronor	1973–88	NEI	0.35	—	0
Nor-Q.D.	1973–88	NEI	0.35	—	0
Ovrette	1974–86	NOR	0.075	—	0
Multiphasic Formulations					
Nelova 10/11	1988	NEI	0.76	EE	35
Ortho-Novum 10/11	1982–88	NEI	0.76	EE	35
Ortho-Novum7/7/7	1984–88	NEI	0.75	EE	35
Triphasil	1984–88	LEV	0.09	EE	32
Tri-Levlen	1986–88	LEV	0.09	EE	40
Tri-Norinyl	1984–88	NEI	0.71	EE	35

[a]Average dose is reported for multiphasic formulations.
CHL = chlormadinone;
DIM = dimethisterone;
ETH = ethynodiol diacetate;
LEV = levonorgestrel;
MED = medroxyprogesterone acetate;
NEA = norethindrone acetate;
NEI = norethindrone;
NEY = norethynodrel;
NOR = norgestrel
EE = ethinyl estradiol;
ME = mestranol